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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/880,038	06/14/2001	Olivier Meyer	032751-049	7218

7590 08/04/2003

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/04/2003

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/880,038	MEYER, OLIVIER	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *22-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5,6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. This Action is in response to the communication filed on5/14/03, as Paper No. 11. Claims 1, 3, 5, 7, 19 and 20 have been amended. Claims 2 and 6 have been cancelled. Claims 1 3-5 and 7-26 are currently pending in the application and are addressed herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Election/Restrictions

3. Claims 22-26 have previously been withdrawn from further consideration for the reasons of record pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8, filed 11/3/02.

4. Additionally, Applicants elected, with traverse the species: Hexadecylphosphocholine (HPC or HePC) and IL-2 in Paper No. 8

5. Claims 1, 3-5 and 7-21 are examined herein.

Claim Rejections - 35 USC § 103

1. Claims 1-21 were rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. (WO 99/05303; published 4 Feb. 1999) in view of Addison et al. (Gene Therapy 1998, 5:1400-1409).

Response to Arguments

2. Applicant's arguments, see page 7-8 of the response filed 5/14/03, with respect to the rejection(s)of claim(s) 1-21 under USC 103(a) have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made for the reasons set forth herein.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 3-5 and 7-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. The claims are indefinite because newly amended claim 1 includes a formula for a compound including groups R_1, R_2, R_3 and R_4 (see claim 1(ii)(A)). Claim 1 defines R_1 as being "either a linear or branched carbon-based chain comprising from 6 to 30 carbon atoms". However, R groups R_2-R_4 are not specifically defined in the claim. It is noted that claim 2 (now cancelled) previously defined R_2-R_4 as being "either hydrogen atoms or alkyl residues

comprising from 1 to 5 carbon atoms". (See previously pending claim 2 on p. 44 lines 1-3 of the specification). In the currently pending claim 1, R groups R_2-R_4 are not defined; therefore, claim 1 is indefinite. Claims 3-5 and 7-21 depend on claim 1 and are rejected for the same reasons.

For examination purposes, R groups R_2-R_4 are considered to be either hydrogen atoms or alkyl residues comprising from 1 to 5 carbon atoms as previously indicated in claim 2 (now cancelled).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 3-5, 7-17, and 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Egilmez et al. (Gene Therapy, Vol. 3, p. 607-614; 1996, cited in IDS) in view of Vehmeyer et al. (Cellular Immunology, Vol. 137, p. 232-238; 1991).

The instant claims are drawn to a combination product comprising a nucleic acid encoding a polypeptide of interest and at least one phospholipid having a particular structural limitation. It is noted that a species election was set forth in a previous Office Action and Applicants elected the following species: IL-2 (as the elected species of polypeptide of interest) and Hexadecylphosphocholine (HePC) (as the elected species of phospholipid) (see Paper No. 8).

Egilmez teaches a composition comprising cationic-liposome nucleic acid complex wherein the nucleic acid comprises a plasmid vector which operably encodes IL-2 (e.g., see abstract and p. 608, column 1). Egilmez teaches that human IL-2 encoding nucleic acid is complexed with DC-cholesterol liposomes (a cationic liposome which associates with the nucleic acid of interest and which is capable of integrating into a liposome) which can be transferred to tumors in vivo resulting in suppression of the tumor growth (e.g., see abstract). Egilmez also indicates that the composition can be diluted in sterile DMEM (a pharmaceutically acceptable vehicle) and then injected into tumors in mice (e.g., see p. 613, second column).

Egilmez does not teach that the composition comprises a phospholipid which meets the structural limitations set forth in the claims, such as Hexadecylphosphocholine (HePC) (the elected species).

However, Vehmeyer teaches Hexadecylphosphocholine (HePC) an antitumor compound having immunostimulatory activity such that it enhances T-cell responses via IFN-gamma induction, but only when HePC is used in combination with IL-2 (e.g., see abstract and p. 232 last paragraph, and p. 233 under "Results") Vehmeyer specifically teaches, "In no case was a significant IFN-g production found in the presence or absence of HePC when IL-2 had been omitted from the cultures" (see p. 233 under "Results")—indicating the critical importance using HePC in combination with IL-2.

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of invention to modify the composition taught by Egilmez such that the composition comprised HePC (in addition to the nucleic acid encoding IL-2 and DC-cholesterol liposome)

wherein the components are formed into a complex that can be delivered to tumors in order to suppress tumor growth with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to combine the teachings of Egilmez and Vehmeyer because Vehmeyer indicates that the combination of HePC and IL-2 induces IFN-g and enhances T-cell antitumor responses (e.g., see abstract and p. 232 last paragraph).

It is noted that claim 1 indicates that the polypeptide and phospholipid of interest have cytotoxic activity. It is respectfully pointed out that the claim is drawn to a product (i.e. a combination product) and the limitation that the polypeptide and phospholipid have cytotoxic activity is merely a functional limitation. Therefore, any composition that meets the structural limitations of the claims would by necessity have the desired function. However, in the instant case, it is clear that the prior art indicates that IL-2 and HePC have cytotoxic activity when used together (e.g., see Vehmeyer, p. 232, abstract).

8. Claims 1, 11, 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Egilmez et al. (Gene Therapy, Vol. 3, p. 607-614; 1996, cited in IDS) in view of Vehmeyer et al. (Cellular Immunology, Vol. 137, p. 232-238; 1991) as applied to claims 1, 11 and 16 above, and further in view of Bischoff (WO 98/08489).

As indicated above, Egilmez teaches a composition comprising cationic-liposome nucleic acid complex wherein the nucleic acid comprises a plasmid vector which operably encodes IL-2 (e.g., see abstract and p. 608, column 1). Egilmez teaches that human IL-2 encoding nucleic acid is complexed with DC-cholesterol liposomes (a cationic liposome which associates with the

nucleic acid of interest and which is capable of integrating into a liposome) which can be transferred to tumors in vivo resulting in suppression of the tumor growth (e.g., see abstract). Egilmez also indicates that the composition can be diluted in sterile DMEM (a pharmaceutically acceptable vehicle) and then injected into tumors in mice (e.g., see p. 613, second column).

Egilmez does not teach that the composition comprises a phospholipid which meets the structural limitations set forth in the claims, such as Hexadecylphosphocholine (HePC) (the elected species).

Vehmeyer teaches Hexadecylphosphocholine (HePC) an antitumor compound having immunostimulatory activity such that it enhances T-cell responses via IFN-gamma induction, but only when HePC is used in combination with IL-2 (e.g., see abstract and p. 232 last paragraph, and p. 233 under "Results"). Vehmeyer specifically teaches, "In no case was a significant IFN-g production found in the presence or absence of HePC when IL-2 had been omitted from the cultures" (see p. 233 under "Results")—indicating the critical importance using HePC in combination with IL-2.

Neither Egilmez nor Vehmeyer teaches that the combination product complex has a charge ratio in the range of 0.05-20 (claim 17) or that complex has a diameter of between 20 and 800nm (claim 18).

However, Bischoff teaches a cationic lipid-nucleic acid complex wherein the cationic lipid is preferably DC-cholesterol (e.g., see p. 10 lines 8-11) and wherein the mean diameter size of the complex is less than 400nm, and in most cases less than 200nm (e.g., see p. 25, lines 5-6 and claim 6); and have a mean charge ratio that preferably are in the range of 1-20 (see p. 14, lines 25-27). Bischoff indicates that the cationic lipid-nucleic acid complexes having a charge

ration in the range of 1-20 and that have a mean diameter less than 400nm were able to deliver the nucleic acid of the complex into cells in vivo (e.g., see Example 3, p. 26-27).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of invention to modify the composition taught by Egilmez such that the composition comprised HePC (in addition to the nucleic acid encoding IL-2 and DC-cholesterol liposome) wherein the components are formed into a complex (as indicated above) and to further modify the composition such that the mean diameter size of the complex was less than 200nm (i.e., in the range of 20 and 800nm) and such that the charge ratio of the complex was in the range of 1-20, with a reasonable expectation of success.

The motivation to modify the complex made by combining the teachings of Egilmez and Vehmeyer is provided by Bischoff who indicates that cationic lipid-nucleic acid complexes have a charge ratio in the range of 1-20 and with a mean diameter size of less than 200nm are able to deliver the nucleic acid encoding polypeptide of interest into cells in vivo. It is noted that Egilmez does not explicitly indicate any particular diameter size for the complex, or any particular charge ratio for the complex.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
July 26, 2003

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER